REMARKS

In a non-final Office Action dated January 28, 2008, the Examiner in charge of the above-identified application withdrew the finality of the previous Office Action in response to applicants filing of a Request for Continued Examination and entered applicants' prior response. As such, Claims 1-17 remain pending. Claims 1-12 and 17 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, and Claims 13-16 are withdrawn from consideration as being directed to a non-elected invention.

At the outset, applicants thank Examiner Celine Qian and Supervisor Joe Woitach for conducting the telephonic interview on April 14, 2008 with the applicants' undersigned representative, and Dr. Victoria Sutton. Applicants found the Examiner interview helpful and informative for resolving the remaining issues in this application.

Briefly, prior to the interview, applicants provided the Examiners with a proposed set of claims to facilitate the interview process. In reviewing the proposed claims, Examiner Qian and Supervisor Woitach noted that additional amendments clarifying the claims and evidence would help to overcome the remaining enablement rejections. For example, it was suggested that Claims 5-8 directed to methods of lowering plasma triglyceride levels be cancelled as the exemplified results are non-conclusive for this embodiment. Also, to maintain consistency with the nomenclature used in the claims of U.S. Patent No. 5,521,071, which is an earlier Dr. Attie case also relating to the soluble LDL receptor and gene and disclosed in the present application, it was suggested that Claims 2, 6, 17 and any new claims be amended to recite "LDL-R^{354}", instead of LDLR354. It was also discussed that the claims clearly indicate that the DNA sequence encoding a fusion protein are operably linked to a promoter for expression in a cell.

The Examiner also suggested that scientific evidence be made of record that the presence of the EGF domain in the LDL receptor fusion protein is immaterial and does not interfere in the lowering of serum cholesterol levels in mammals. Applicants were also asked to provide other possible uses for the claimed construct.

Accordingly, applicants agreed to revise the proposed claims and prepare a response reflective of the contents of the interview. As such, applicants respond by submitting the

amendments above, and comments set forth hereinbelow. Based on this submission, reconsideration of the merits of this patent application is respectfully requested, followed by a Notice of Allowance.

Claim Amendments

Applicants have elected to cancel without prejudice Claims 5-8 directed to methods of lowering plasma triglyceride levels and previously withdrawn Claims 13-16 to expedite prosecution on the merits. Applicants reserve the right to pursue prosecution of these claims in a continuing-type application.

Claims 1 and 9, specifically the steps of making the genetic construct and delivering it into a vein of a mammal, are amended to recite instead preparing a nucleic acid construct and administering the construct systemically to the mammal. Claims 2, 6, 17 and the new claims are amended to now recite "LDL-R^{354}", instead of LDLR354. Also, Claims 1, 9, and 17 are amended to clarify the nucleic acid construct comprises a DNA sequence encoding a fusion protein operably linked to a promoter for expression in a cell. These claims make clear that the construct is administered systemically to lower serum cholesterol levels. In these claims, the truncated soluble LDLR is defined broadly as including the LDL binding domain, but not the membrane domain or the O-linked sugar domain.

As noted above, new Claim 18 is added, drawn to a *nucleic acid construct* for the lowering of serum cholesterol levels. Also new Claims 19 and 20 are added, drawn to a *method* for the lowering of serum cholesterol levels. The new claims recite LDL-R^{354} as the truncated LDL receptor and specify localization domain signal peptides. The new claims are added for the Examiner's consideration, not to limit the claims, but to identify and establish allowable subject matter. No new matter is added.

Support for the claim amendments are found throughout the specification at, for example, Figures 1 and 2; pg. 3, lines 25-29; pg. 4, lines 1-5 and line 10-15; pg. 5, lines 25-30; and pg. 8-9, relating to the results of *in vitro* and *in vivo* experiments. In view of these amendments,

applicants respectfully request reconsideration and withdrawal of the objections and rejections issued in this application.

Claim Rejections - 35 USC §112, first paragraph

Claims 1-12 and 17 are rejected under 35 U.S.C. 112, 1st ¶ for allegedly lacking enablement. The Examiner asserts at pages 3-4 of the Action that "[A]pplicants fail to demonstrate that the claimed invention has overcome the art recognized obstacles and successfully lowered serum cholesterol and plasma triglyceride in human patients." Applicants respectfully wish to traverse this rejection.

However, to expedite prosecution of the claims on the merits of the invention, and without agreeing or acquiescing to the rejection, applicants have cancelled without prejudice Claims 5-8 relating to lowering plasma triglyceride levels. Applicants reserve the right to pursue prosecution of these claims in a continuing-type application.

Also, applicants have amended the claims as noted above to ensure that the claims fully comply with the enablement requirement.

Further in regards to demonstrating that the examples enable practicing the invention in human patients, applicants draw the Examiner's attention to the statement in the specification that "[F]or human, mice are a recognized animal model for testing of LDL lowering strategies." (See specification, pg. 5, lines 19-20). Applicants go on to provide that

> "[T]he result is achieved whether or not the cells are treated *in vitro* or *in vivo*, provided only that an expression system appropriate for the host is chosen. As the data below demonstrates, it is possible to introduce an expression construct for the LDLR/localization domain fusion protein into an individual *in vivo* with the result that meaningful decreases in apoB levels are observed. Thus treatment of individuals, as well as cells, is contemplated." (See specification, pg. 5, lines 25-30).

Accordingly, it is believed that the amended claims are fully enabled and the rejection is now moot.

As noted above, during the interview the Examiner suggested that the role of the epidermal growth factor (EGF) precursor in the LDL receptor protein be more clearly defined on

the record. At the outset, applicants submit that the truncated form of the LDLR recited in the claims includes the repeat sequences at the amino terminus of the protein, which provides the LDL binding function, without the need for the other LDL-related domains, namely without the presence of EGF precursor domain, carbohydrate domain or membrane binding domain. To the truncated LDLR protein, a localization domain was added to retain the fusion protein inside of the cell (see Specification, pg. 4,1st paragraph). As such, the truncated LDLR is not passed to the extracellular surface, but can effectively bind to LDL (see, specification, pg. 4, lines 10-15).

Notably, in Dr. Attie's earlier patent relating to the LDL receptor (U.S. Patent No. 5,521,071, see specification and pg. 3, line 29, and pg. 6, line 2 under Examples), the EGF precursor homology domain is not required or included in the truncated form of the human LDL receptor, which is defined as playing a role in the acid-dependent disassociation (release) of the lipoproteins from the receptor, during receptor recycling. The '071 patent, also indicates that the EGF domain serves to position the ligand-binding domain, so that it can bind LDL on the cell surface.

More recently, the crystal structure of the LDL receptor extracellular domain at endosomal pH was studied. (See, Rudenko et al., *Science* vol. 298 pg. 2353-2358 (2002); submitted in a Supplemental Information Disclosure Statement herewith). Rudenko et al. showed that the EGF domain is not required for binding lipoprotein particles. EGF is required for ligand release. Specifically, mutant LDL-R and VLDL-R lacking the complete EGF precursor homology domain still bind a ligand at the cell surface (though with reduced affinity for LDL) and are internalized but fail to recycle (See also, Davis et al., *Nature* 326, 760 (1987); submitted in a Supplemental Information Disclosure Statement herewith). Therefore, based on the above, applicants believe that the role of EGF is immaterial to the claimed invention and that the EGF domain does not interfere with the lowering of serum cholesterol levels in a mammal.

As to the Examiner's suggestion that other uses for the nucleic acid construct be provided on the record, applicants submit that there are a number of experimental (research tool) uses for the claimed constructs. For example, it is known that the LDL receptor plays a role in viral entry (bovine viral diarrhea virus and hepatitis C virus) into a cell. (See for example, Agnello et al.

PNAS 96:22 pgs. 12766-12771 (1999); submitted in a Supplemental Information Disclosure Statement herewith). Based on this knowledge, the claimed nucleic acid construct, having an LDLR fusion protein, may be used to analyze the nature of binding viral proteins or as a screen to identify small molecules that block the infection of mammalian cells by hepatitis C. Also, the nucleic acid construct can be used as a vector for protein production. Alternatively, the construct can be used to study the effect of human LDL receptor overexpression on various cells and cell lines. The construct can also serve as an initial screening tool to look at the effect of various small molecule agents on LDL receptor expression and response. Based on these comments and the amendments above, applicants believe that they have addressed the Examiner's concerns regarding the claims and that this rejection is now moot.

Summary

Applicants have made a diligent effort to place the claims in condition for allowance. However, should there remain unresolved issues that require adverse action, it is respectfully requested that the Examiner telephone applicants' attorney at the number listed below so that such issues may be resolved as expeditiously as possible. For the reasons stated above this application is now considered to be in condition for allowance and such action is earnestly solicited.

Fees

A petition for an extension of time is submitted herewith so this response will be considered timely filed. Also, applicants submit a Supplemental Information Disclosure Statement herewith. Please charge the fees in connection with both to Deposit Account No. 17-0055. If any other fee is due or any other extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the fees to the Deposit Account No. 17-0055.

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